## Re: Environmental Tobacco Smoke, Genetic Susceptibility, and Risk of Lung Cancer in Never-Smoking Women

Bennett et al. *(1)* report that never-smoking Missouri women who report exposure to environmental tobacco smoke (ETS) and develop lung cancer are more likely to be deficient in GSTM1 activity (GSTM1 null genotype) compared with never smokers who had no ETS exposure and developed lung cancer (odds ratio [OR] = 2.6; 95% confidence interval [CI] = 1.1–6.1). It is further concluded that "For the half of the population of never-smoking women with the GSTM1 null polymorphism, ETS exposure is responsible for between 42% and 49% of the lung cancer cases."

Yet in an accompanying editorial, Weinberg and Sandler *(2)* comment: "Clearly, many questions remain, and the reported interaction *(1)* between GSTM1 and ETS requires confirmation." They also point out that an OR of 2.6 for the association of ETS exposure with lung cancer in GSTM1 null nonsmoking women suggests a relative risk of at least 1.7 for the association of ETS with lung cancer in nonsmoking women, which is inconsistent with generally accepted estimates *(3)*, including the reported OR of 1.1 (95% CI = 0.8–1.3) for Missouri women *(4)*.

The International Agency for Research on Cancer has investigated genetic polymorphisms of GSTM1 and GSTT1 in nonsmokers and their interaction with exposure to ETS in a multicenter case–control study of 115 nonsmoking lung cancer case subjects, in 177 smoking lung cancer case subjects, and in 109 nonsmoking hospital or population control subjects *(5)*. The GSTM1 null genotype was not associated with risk of lung cancer in nonsmokers (OR = 0.97; 95% CI = 0.55–1.72) and with a modest, not statistically significant, increase in risk in smokers (OR = 1.70; 95% CI = 0.71–4.05). GSTT1 null genotypes were associated with decreased risk in both nonsmokers (OR = 0.65; 95% CI = 0.35–1.19) and smokers (OR = 0.92; 95% CI = 0.34–2.48). Nonsmoking case subjects experienced higher levels of ETS exposure than control subjects. It was concluded that "These results do not suggest a role of GST M1 or T1 polymorphisms as modifying factors of lung cancer risk due to ETS exposure in nonsmokers."

Further, Nyberg et al. *(6)*, in a study of 185 male and female nonsmoking and smoking lung cancer patients and 164 frequency-matched population control subjects, reported an overall OR for lung cancer associated with the GSTM1 null genotype of 0.8 (95% CI = 0.5–1.2), with an OR close to unity among ever smokers (OR = 0.9; 95% CI = 0.4–1.9) and lower among never smokers (OR = 0.6; 95% CI = 0.3–1.1). The risk of lung cancer was almost identical among never smokers reporting exposure to ETS from the spouse or at work during the last 10 years before diagnosis (OR = 0.7; 95% CI = 0.2–1.9) and those reporting no exposure to ETS (OR = 0.6; 95% CI = 0.2–1.0).

Clearly, epidemiologic approaches that use either case-only *(1)* or case–control *(5,6)* designs differ, making it hard to conclude whether individuals with germline polymorphisms in genes for enzymes that detoxify environmental genotoxins are at increased risk of lung cancer due to exposure to ETS.

ANTHONY R. TRICKER

### REFERENCES


*(1)* Bennett WP, Alavanja MC, Blomeke B, Vahakangas KH, Castren K, Welsh JA, et al. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. J Natl Cancer Inst 1999;91:2009–14.

*(2)* Weinberg CR, Sandler DP. Gene-by-environment interaction for passive smoking and glutathione *S*-transferase M1? [editorial]. J Natl Cancer Inst 1999;91:1985–6.

*(3)* Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980–8.

*(4)* Brownson RC, Alavanja MC, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. Am J Public Health 1992;82:1525–30.

*(5)* Malats N, Camus-Randon AM, Nyberg F, Ahrens W, Constantinescu V, Mukeria A, et al. Does GST M1 and T1 gene polymorphism modify environmental tobacco smoke effect on lung cancer? [abstract] Proc Am Assoc Cancer Res 1998;39:182.

*(6)* Nyberg F, Hou SM, Hemminki K, Lambert B, Pershagen G. Glutathione *S*-transferase mu1 and *N*-acetyltransferase 2 genetic polymorphisms and exposure to tobacco smoke in nonsmoking and smoking lung cancer patients and population controls. Cancer Epidemiol Biomarkers Prev 1998;7:875–83.


### NOTES

*Editor's note:* A. R. Tricker is employed by the tobacco industry.

*Correspondence to:* Anthony R. Tricker, Ph.D., Philip Morris Europe, Worldwide Scientific Affairs, CH 2003 Neuchâtel, Switzerland.

### RESPONSE

Tricker's only valid criticism cites two negative studies *(1,2)* to refute our observation *(3)*. Although the discrepancy is unexplained, early reports often conflict, and differences are usually reconciled by environmental, genetic, and lifestyle factors. For example, α-tocopherol supplements may compensate for deficient GSTM1 activity *(4)*, and dietary habits are known to modify risks of lung cancer. Therefore, culinary preferences might explain the discordant results, because our analyses *(3)* were adjusted for dietary intakes of fruits and vegetables, but those of Nyberg et al. *(2)* were not. [The abstract report by Malats et al. *(1)* cannot be assessed on this point.] Furthermore, gene–gene interactions between GSTM1 and CYP1A1

modulate risks in Japanese smokers [reviewed in *(5)*], and similar interactions among different genes are likely to occur in Caucasian nonsmokers.

Tricker attacks our point estimate of the interaction odds ratio (OR) for GSTM1 deletion and environmental tobacco smoke exposure by use of a misleading partial quotation from the editorial by Weinberg and Sandler *(6)*. He misrepresents a paragraph in which they begin with the question, "How credible is this number?" (i.e., OR = 2.6), consider two sets of assumptions and analytic approaches, and conclude with "the confidence interval provided . . . for the interaction estimate of 2.6 *does* [emphasis in the original] include numbers as low as this [1.36], which is reassuring."

Tricker asserts that our findings require corroboration, and we fully agree that "additional studies are needed to confirm these observations," as stated in our report *(3)*. Tricker summarizes his criticisms by declaring "it [is] hard to conclude whether individuals with germline polymorphisms in genes for enzymes that detoxify environmental genotoxins are at increased risk of lung cancer due to exposure to ETS [environmental tobacco smoke]." We agree that these studies are technically demanding. In fact, recognizing that "even small errors in the assessment of environmental or genetic factors can result in biased interaction parameters and substantially increased sample requirements" *(7)*, corroboration of an effect linking GSTM1, environmental tobacco smoke, and risk of lung cancer will require substantially larger studies with detailed assessments of exposure and potentially confounding factors.

WILLIAM P. BENNETT
MICHAEL C. R. ALAVANJA
CURTIS C. HARRIS

## REFERENCES

*(1)* Malats N, Camus-Randon AM, Nyberg F, Ahrens W, Constantinescu V, Mukeria A, et al. Does GST M1 and T1 gene polymorphism modify environmental tobacco smoke effect on lung cancer? [abstract]. Proc Am Assoc Cancer Res 1998;39:182.

*(2)* Nyberg F, Hou SM, Hemminki K, Lambert B, Pershagen G. Glutathione *S*-transferase mu1 and *N*-acetyltransferase 2 genetic polymorphisms and exposure to tobacco smoke in nonsmoking and smoking lung cancer patients and population controls. Cancer Epidemiol Biomarkers Prev 1998;7:875–83.

*(3)* Bennett WP, Alavanja MC, Blomeke B, Vahakangas KH, Castren K, Welsh JA, et al. Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. J Natl Cancer Inst 1999;91:2009–14.

*(4)* Woodson K, Stewart C, Barrett M, Bhat NK, Virtamo J, Taylor PR, et al. Effect of vitamin intervention on the relationship between GSTM1, smoking, and lung cancer risk among male smokers. Cancer Epidemiol Biomarkers Prev 1999;8:965–70.

*(5)* Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev 2000;9:3–28.

*(6)* Weinberg CR, Sandler DP. Gene-by-environment interaction for passive smoking and glutathione *S*-transferase M1? [editorial]. J Natl Cancer Inst 1999;91:1985–6.

*(7)* Garcia-Closas M, Rothman N, Lubin J. Misclassification in case–control studies of gene–environment interactions: assessment of bias and sample size. Cancer Epidemiol Biomarkers Prev 1999;8:1043–50.

## NOTES

W. P. Bennett and M. C. Alavanja contributed equally to the preparation of this correspondence.

*Affiliations of authors:* W. P. Bennett, Division of Molecular Medicine, City of Hope Cancer Center and Beckman Research Institute, Duarte, CA; M. C. R. Alavanja (Division of Cancer Epidemiology and Genetics), C. C. Harris (Division of Basic Sciences), National Cancer Institute, Bethesda, MD.

*Correspondence to:* William P. Bennett, M.D., Division of Molecular Medicine, City of Hope Cancer Center and Beckman Research Institute, Fox Plaza S., Rm. 1001A, 1500 E. Duarte Rd., Duarte, CA 91010–3000 (e-mail: bbennett@coh.org).